Biosynthesis of Adrenocortical Hormones

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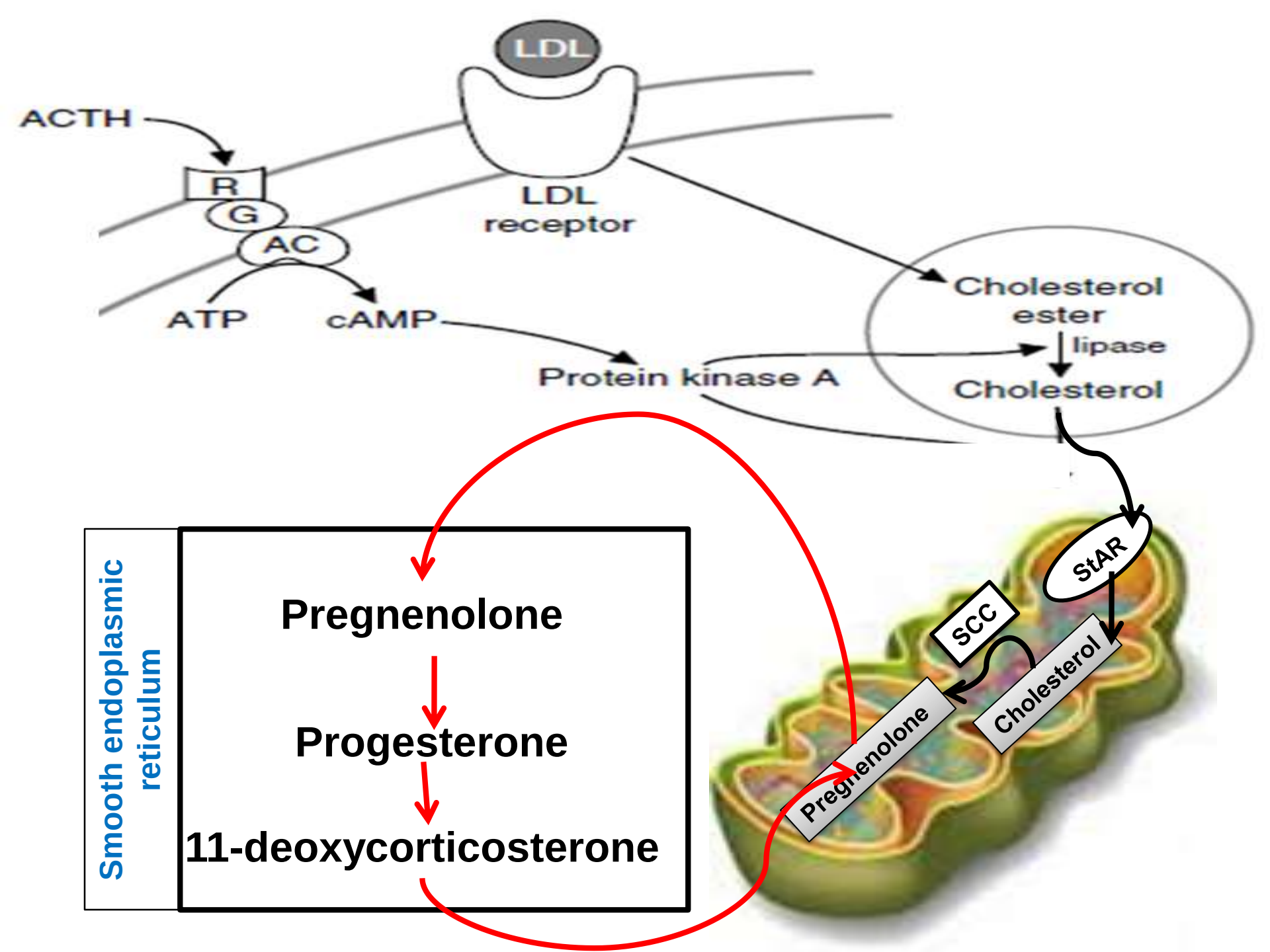
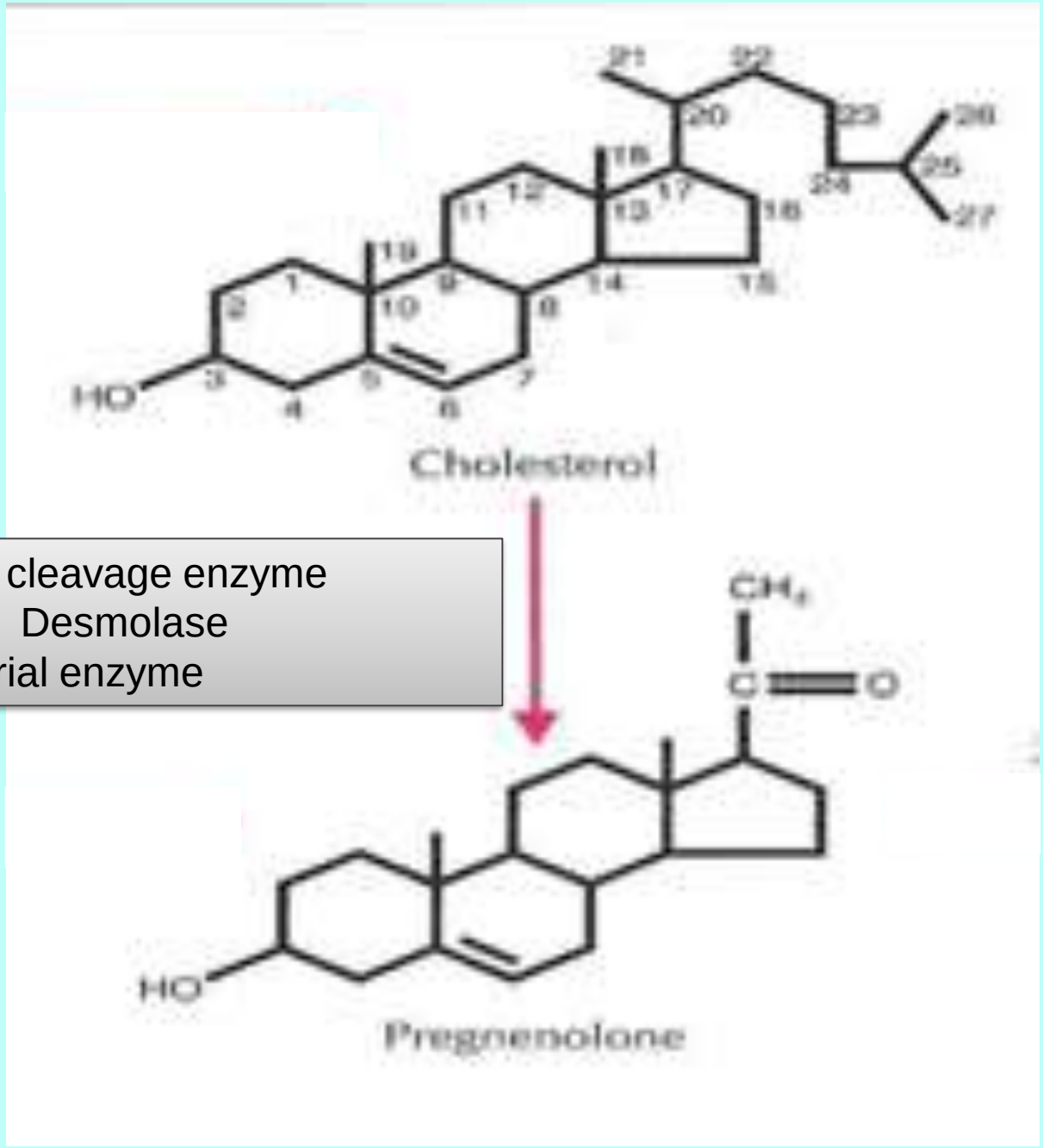
Biosynthesis of Adrenocortical Hormones

- Peptide hormones are encoded by specific genes
- No gene for steroid hormones
- Steroid hormones are synthesized from the enzymatic modification of cholesterol

Biosynthesis of Adrenocortical Hormones

- The 1st enzymatic reaction starting from cholesterol occurs in mitochondria
- Transport of free cholesterol from cytosol to mitochondria is the rate-limiting step in this process
- This rate limiting step is regulated by expression and phosphorylation of the Steroidogenic Acute Regulatory Protein (StAR)

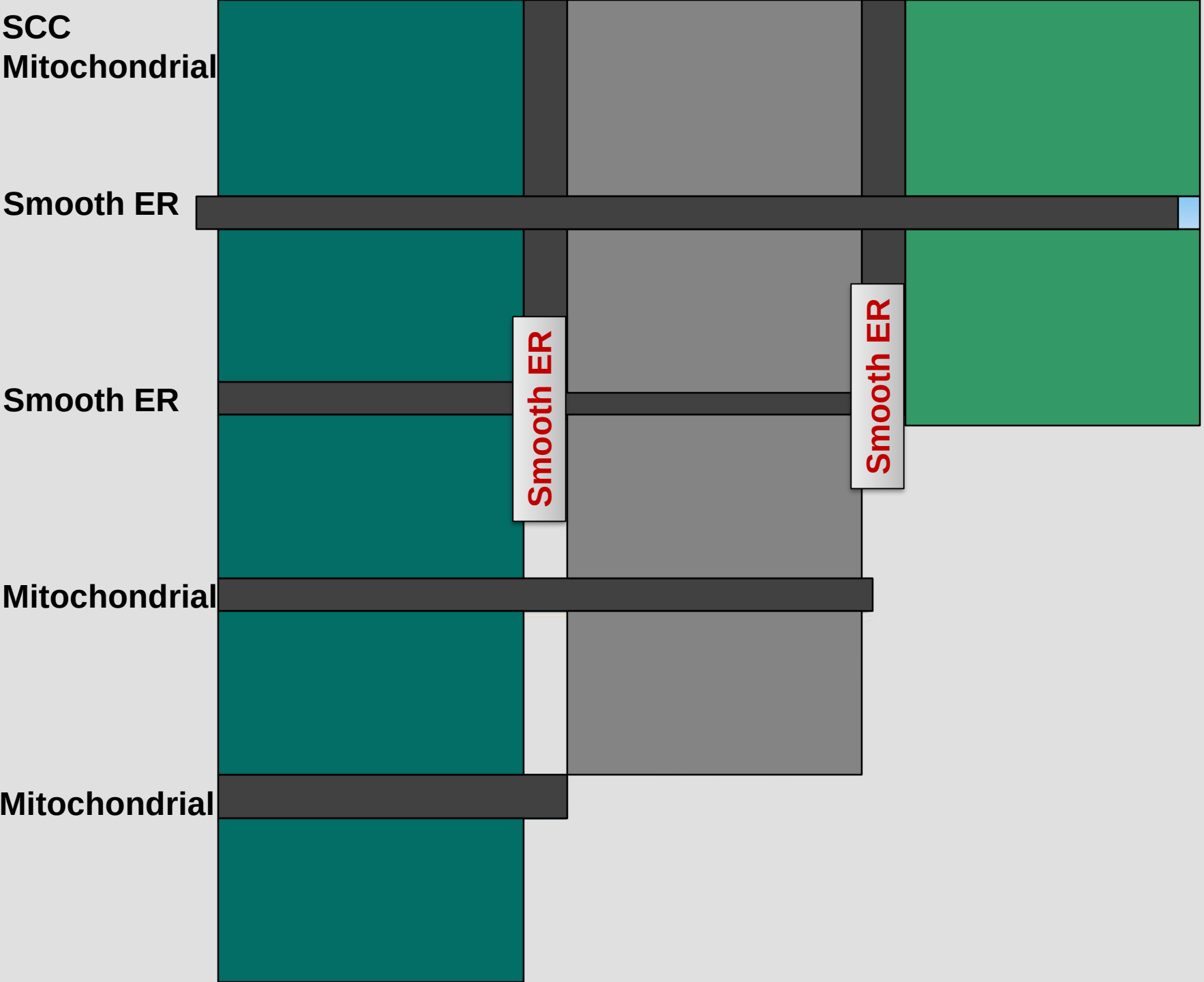

LDL
ACTH
R
G
AC
LDL
receptor
ATP
cAMP
Protein kinase A
Cholesterol
ester
lipase
Cholesterol
Smooth endoplasmic
reticulum
Pregnenolone
Progesterone
11-deoxycorticosterone
StAR
SCC
Cholesterol
Pregnenolone


Cholesterol
Side chain cleavage enzyme
Or Desmolase
Mitochondrial enzyme
Pregnenolone

Biosynthesis of Adrenocortical Hormones

- Pregnenolone comes out of mitochondria and acts as a precursor for three pathways occurring in different zones having different sets of enzymes

  – Aldosterone pathway
    - Zona glomeruloza
  – Cortisol pathway
    - Zona fasciculata
  – Androgens pathway
    - Zona reticularis


SCC Mitochondrial
Smooth ER
Smooth ER
Smooth ER
Smooth ER
Mitochondrial
Mitochondrial

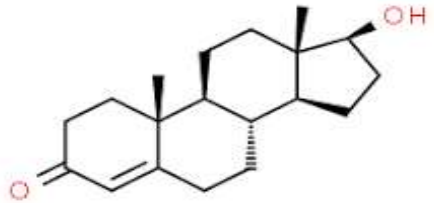
In the zona glomerulosa, which does not have the smooth endoplasmic reticulum

21-Hydroxylase is a smooth endoplasmic reticulum enzyme, whereas 11β-hydroxylase is a ochondrial enzyme. Steroidogenesis thus olves the repeated shuttling of substrates into out of the mitochondria.

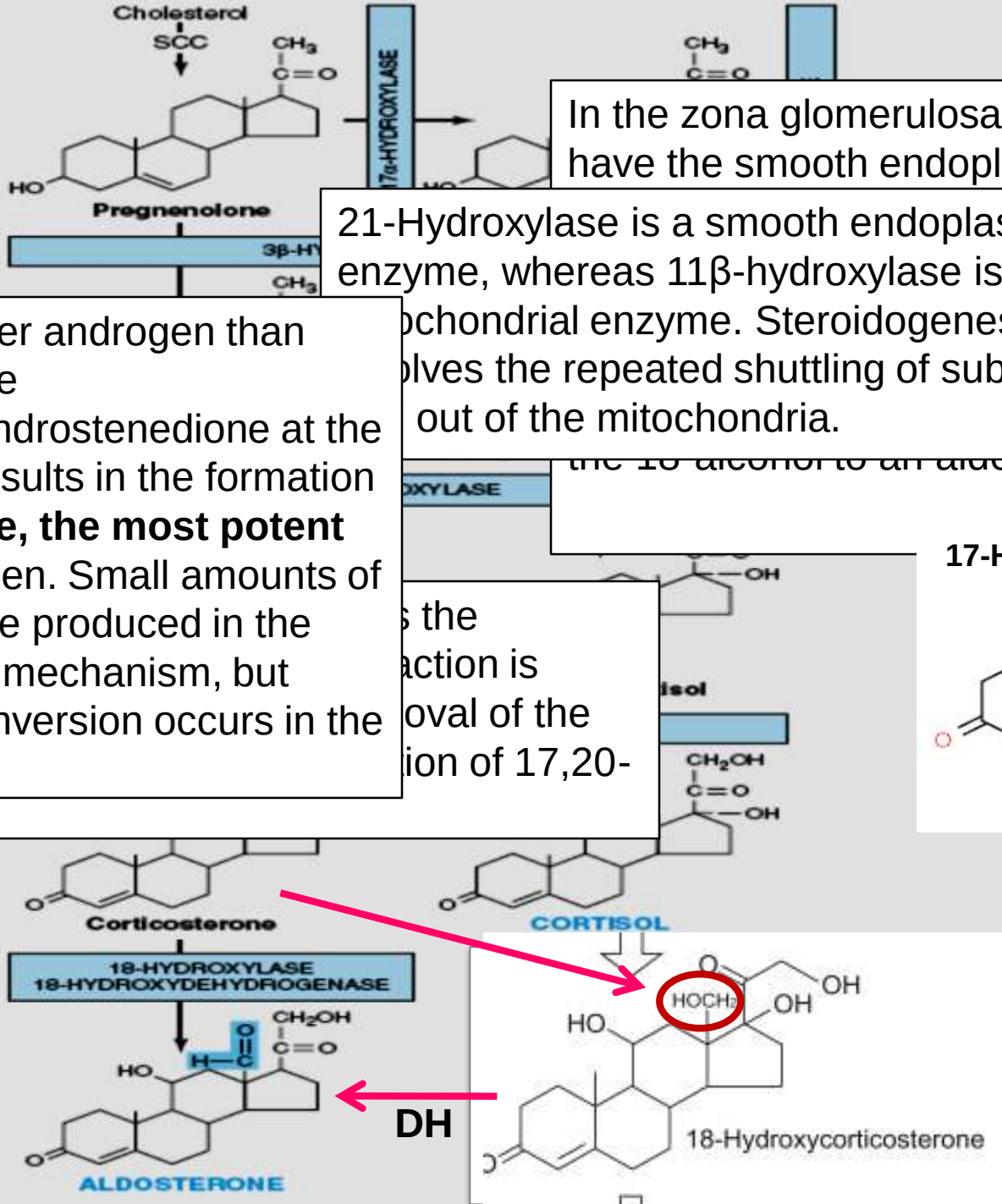
DHEA is weaker androgen than andostenedione
Reduction of androstenedione at the C17 position results in the formation of **testosterone, the most potent** adrenal androgen. Small amounts of testosterone are produced in the adrenal by this mechanism, but most of this conversion occurs in the testes.

s the action is oval of the ion of 17,20-lyase.

17-Hydroxysteroid DH



Testosterone



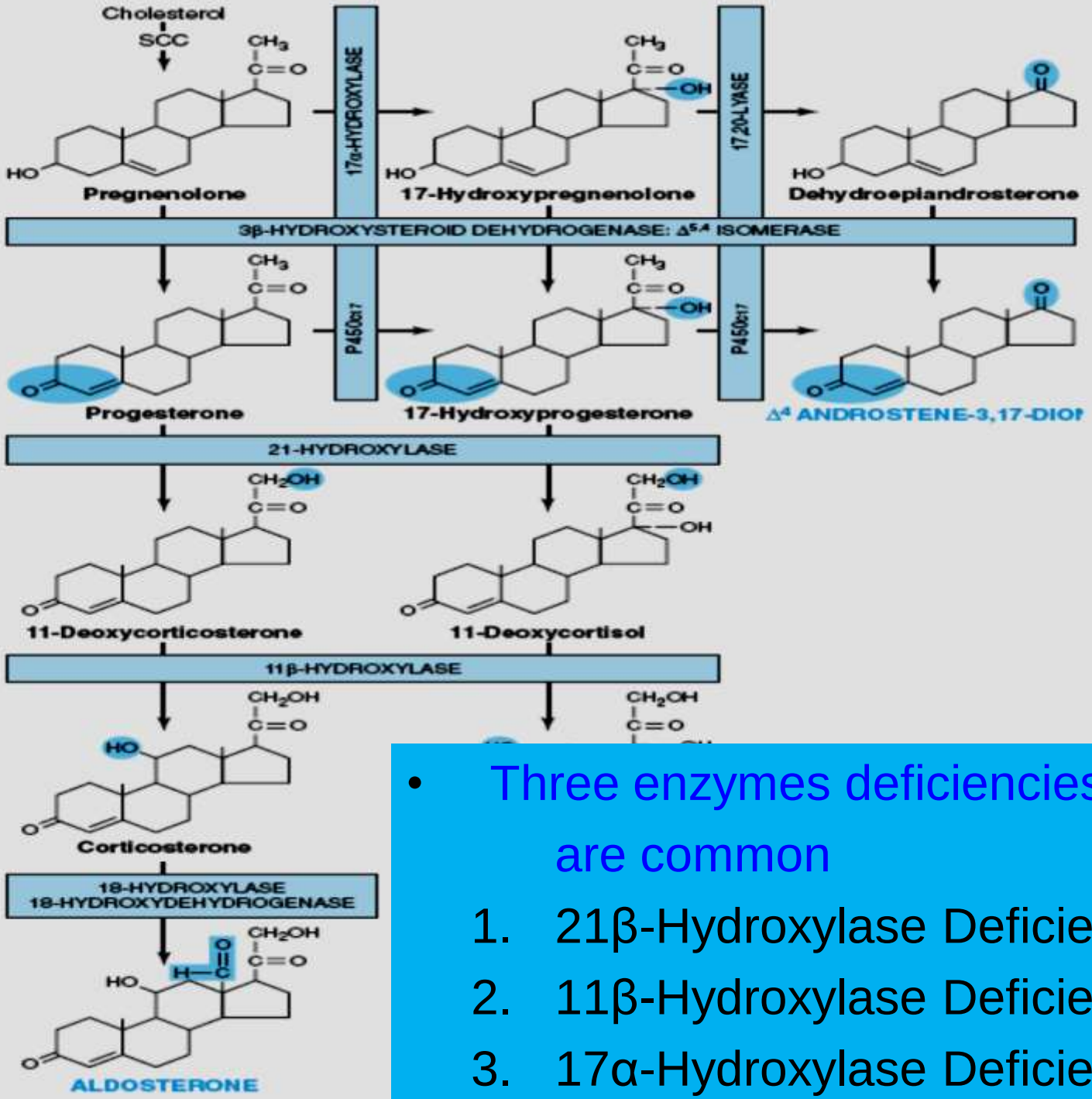
ry for both
orticoid activity,
hydroxy group
less

18- Hydroxy Corticosterone

Enzyme deficiencies

- Single enzyme defects can occur as congenital "inborn errors of metabolism.“
- Congenital defects in any of the enzymes leads to deficient cortisol secretion and the syndrome called ***congenital Adrenal hyperplasia,***

Enzyme deficiencies



- Three enzymes deficiencies are common
  1. 21β-Hydroxylase Deficiency
  2. 11β-Hydroxylase Deficiency
  3. 17α-Hydroxylase Deficiency

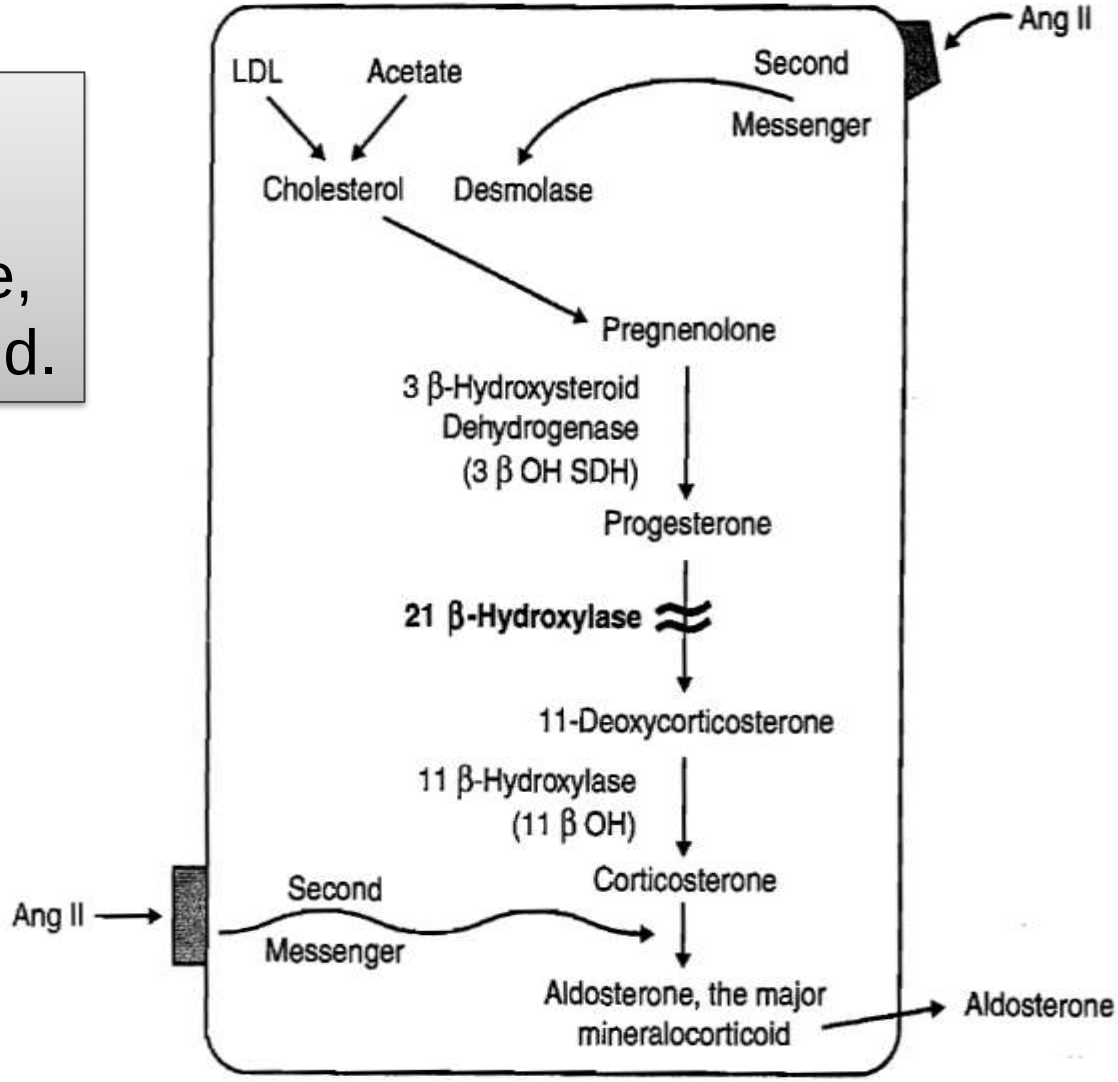
21β-Hydroxylase Deficiency

- Tissues affected:
  - zona glomerulosa
  - zona fasciculata
  - zona reticularis.

Effect in the Zona Glomerulosa

Consequence

The result is decreased production of aldosterone, the main mineralocorticoid.



Consequences

Decreased production of 11-deoxycorticosterone, a weak mineralocorticoid.

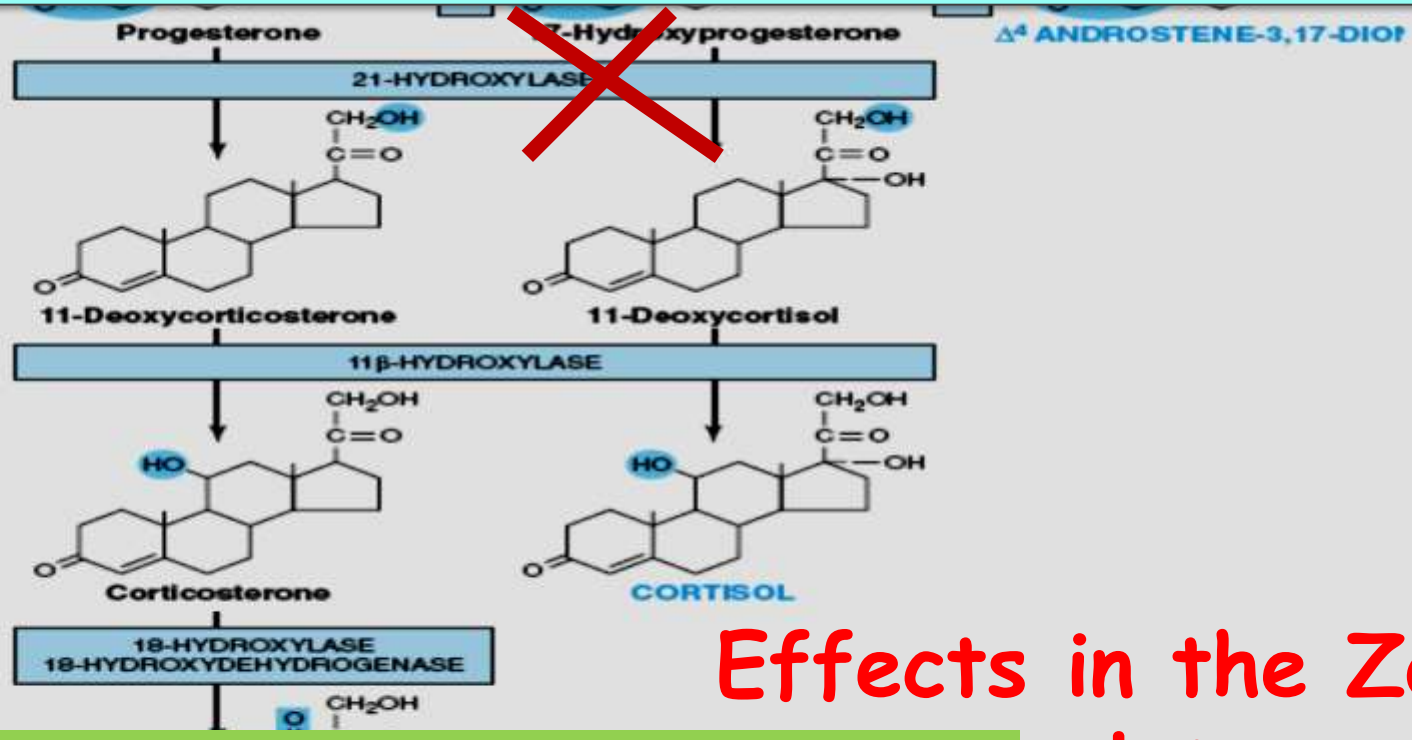
Therefore, a major problem with this disorder is mineralocorticoid deficiency, which results in the following:

Loss of Na+

Decrease in the extracellular volume

Decreased blood pressure

Increased renin secretion by the kidney and increased circulating angiotensin II.

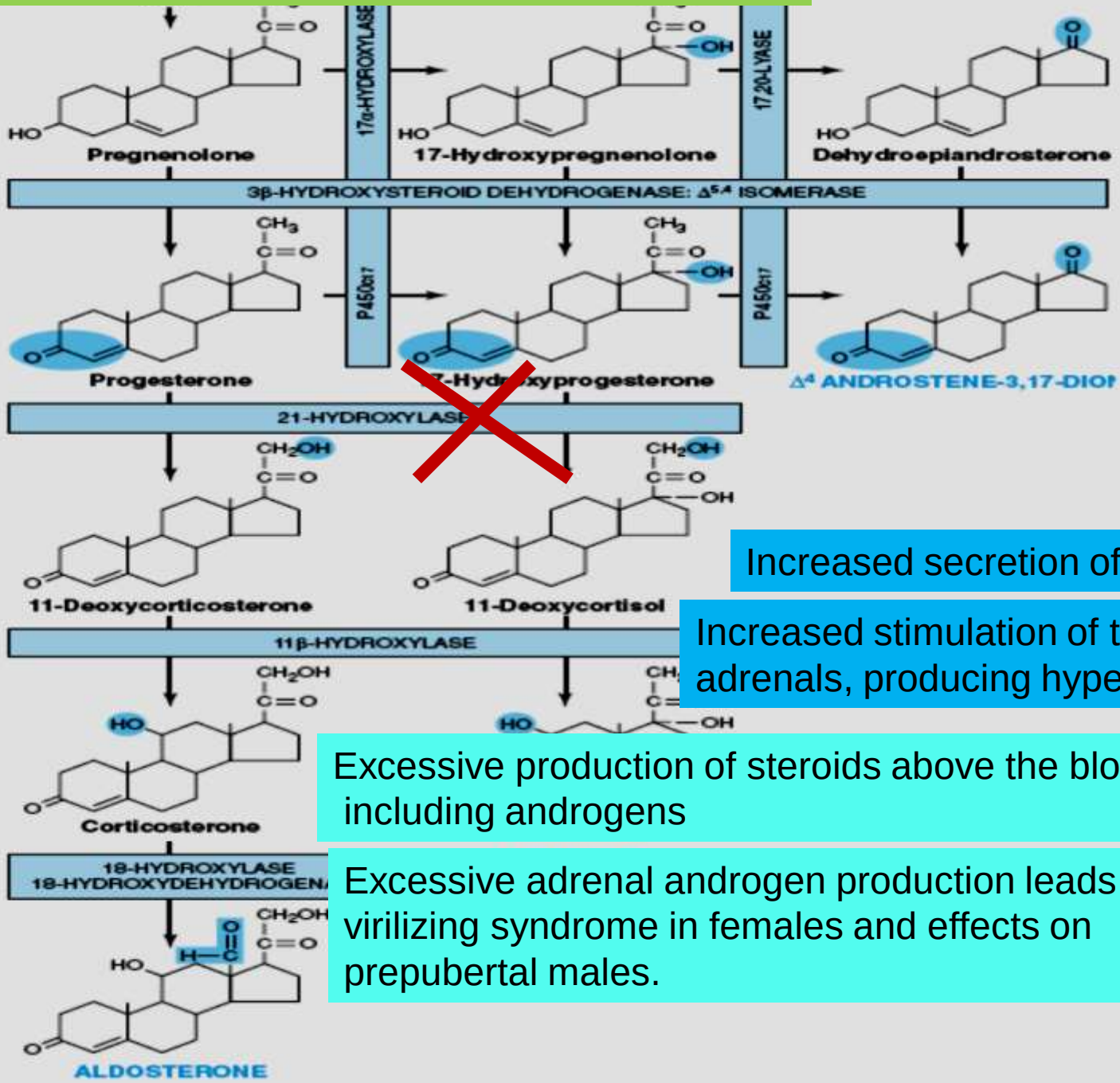


Effects in the Zona culata and Reticularis

Decreased production of corticosterone, a weak glucocorticoid, and cortisol, the main glucocorticoid.

Therefore, another problem is glucocorticoid deficiency.

Loss of feedback on the pituitary by cortisol, which causes:



Increased secretion of ACTH

Increased stimulation of the adrenals, producing hyperplasia

Excessive production of steroids above the blockade, including androgens

Excessive adrenal androgen production leads to the virilizing syndrome in females and effects on prepubertal males.

11β-Hydroxylase Deficiency

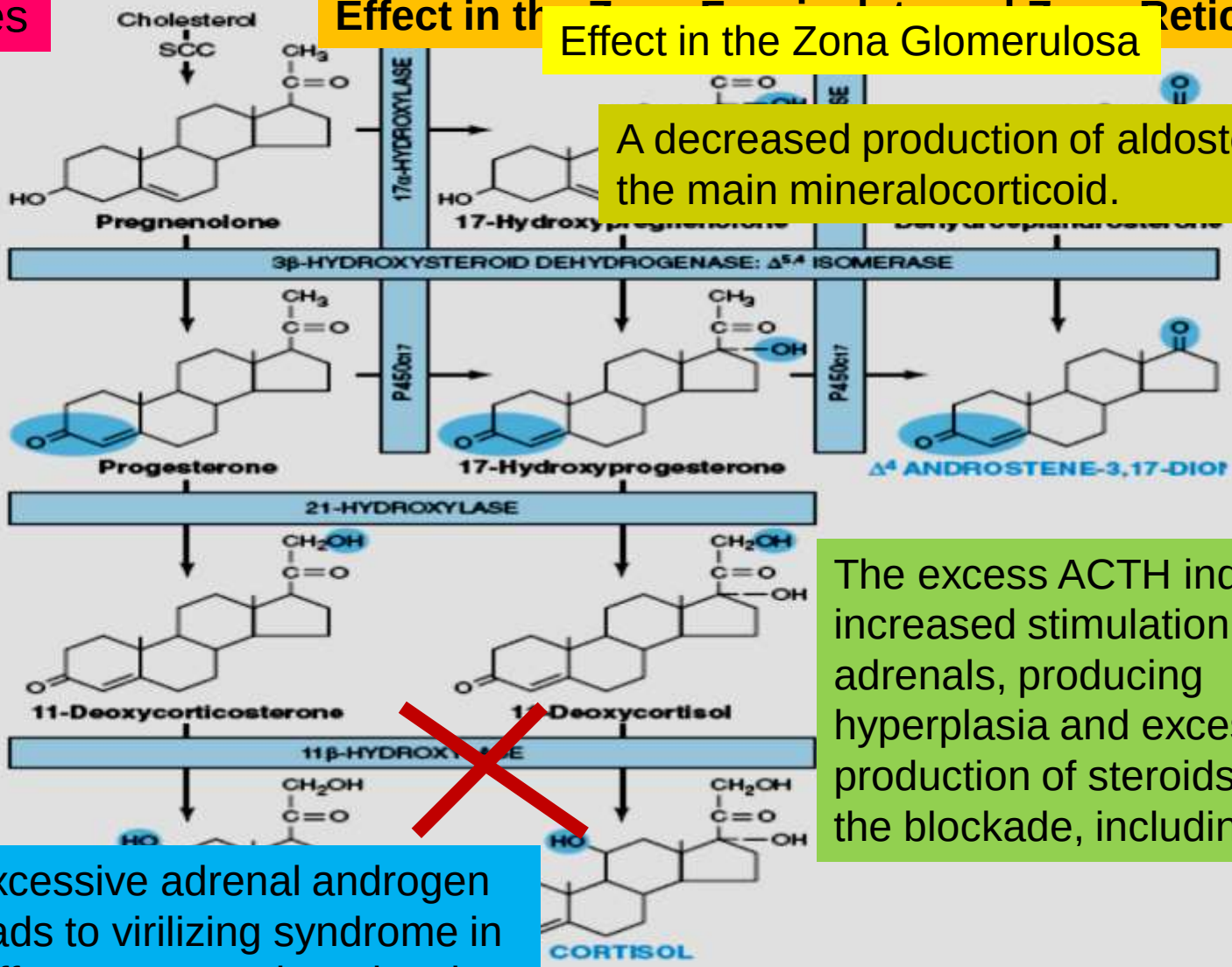
- Tissues affected:
  - zona fasciculata
  - zona reticularis
  - zona glomerulosa

Consequences

Effect in th… Reticularis

Effect in the Zona Glomerulosa

A decreased production of aldosterone, the main mineralocorticoid.



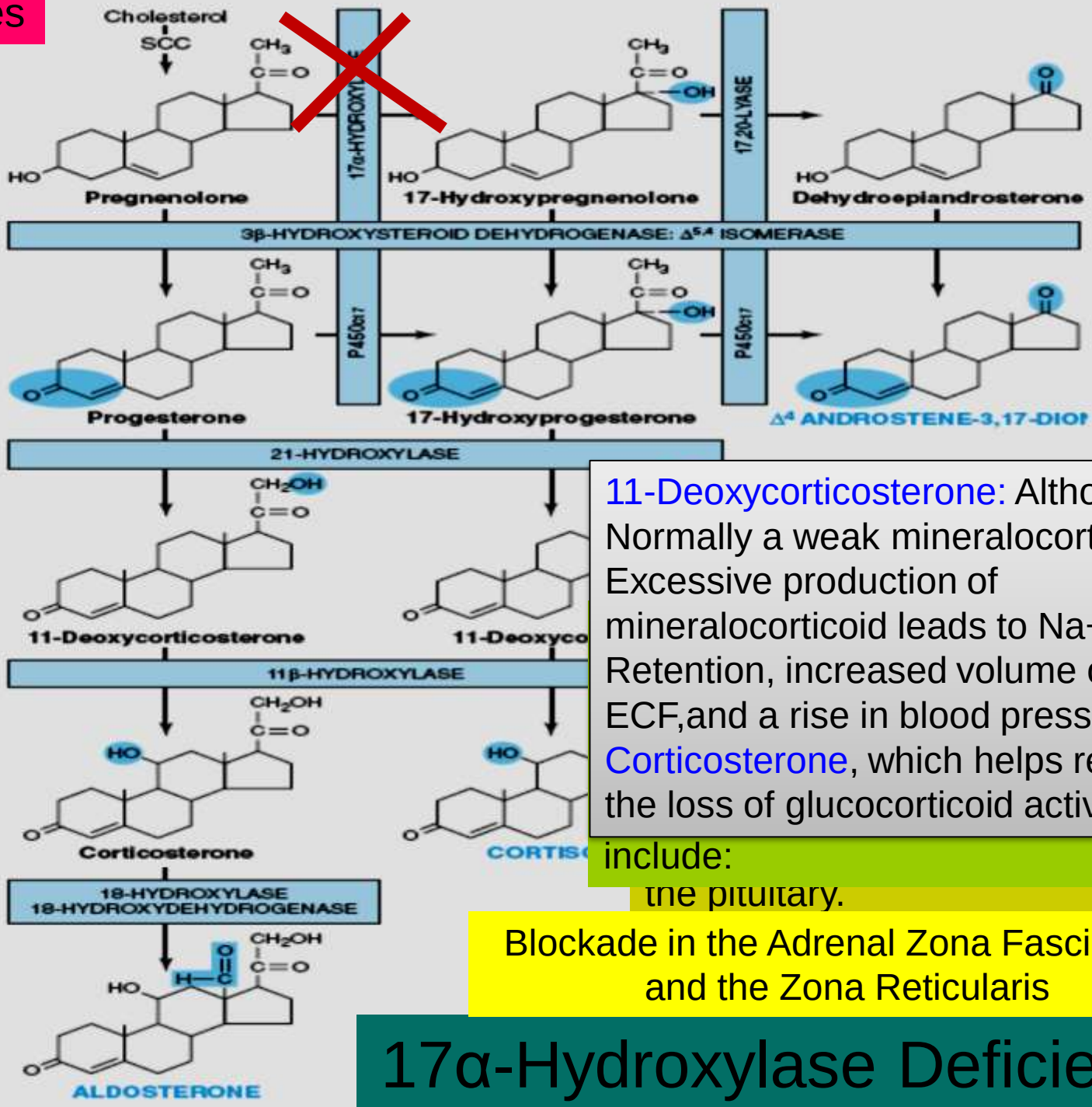
The excess ACTH induces increased stimulation of the adrenals, producing hyperplasia and excessive production of steroids above the blockade, including:

Androgens. Excessive adrenal androgen production leads to virilizing syndrome in females and effects on prepubertal males.

11-Deoxycorticosterone, normally a weak mineralocorticoid
Excessive mineralocorticoid leads to Na+ retention, increased volume of ECF,and a rise in blood pressure.
The rise in blood pressure reduces plasma renin and angotensin II.

…orticosterone, …cortisol, resulting in …H due to loss of

Consequences



11-Deoxycorticosterone: Although Normally a weak mineralocorticoid, Excessive production of mineralocorticoid leads to Na+ Retention, increased volume of ECF,and a rise in blood pressure. Corticosterone, which helps replace the loss of glucocorticoid activity.

include:

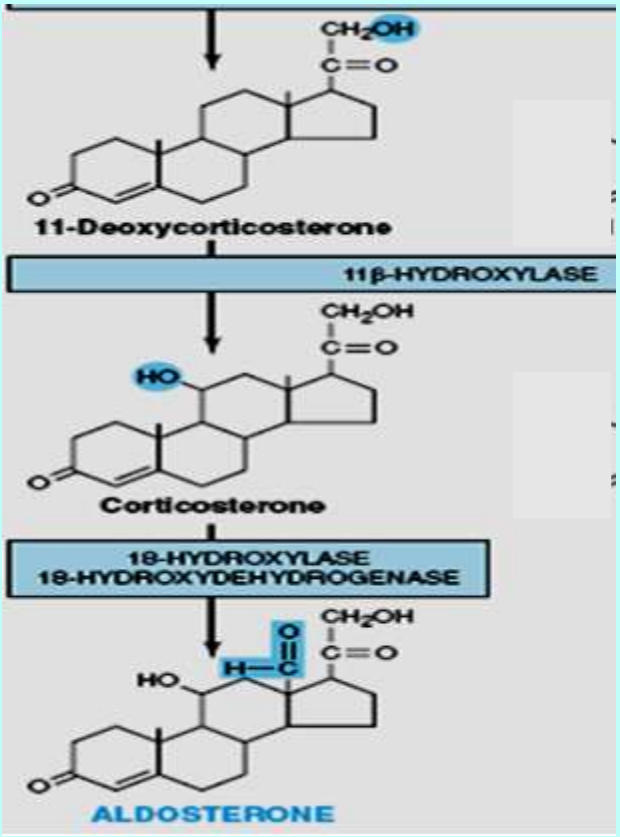
the pituitary.

Blockade in the Adrenal Zona Fasciculata and the Zona Reticularis

17α-Hydroxylase Deficiency

Check Point

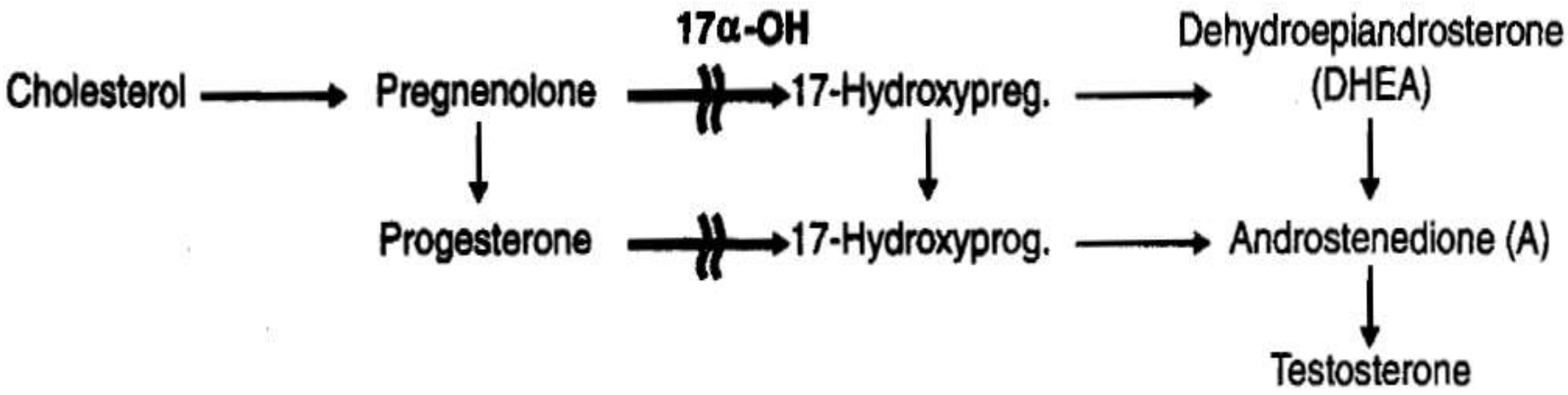
RAAS suppression



- In 17α-Hydroxylase deficiency, there is excessive production of steroids before the blockade. These steroids include:
- 11-Deoxycorticosterone: Although normally a weak mineralocorticoid, excessive production of mineralocorticoid leads to Na+ retention
- Corticosterone: which helps replace the loss of glucocorticoid activity

Why is there no excessive production of aldosterone while it is downstream to these two hormones which are now in excess?

17α-Hydroxylase Deficiency
Effect in the Testes

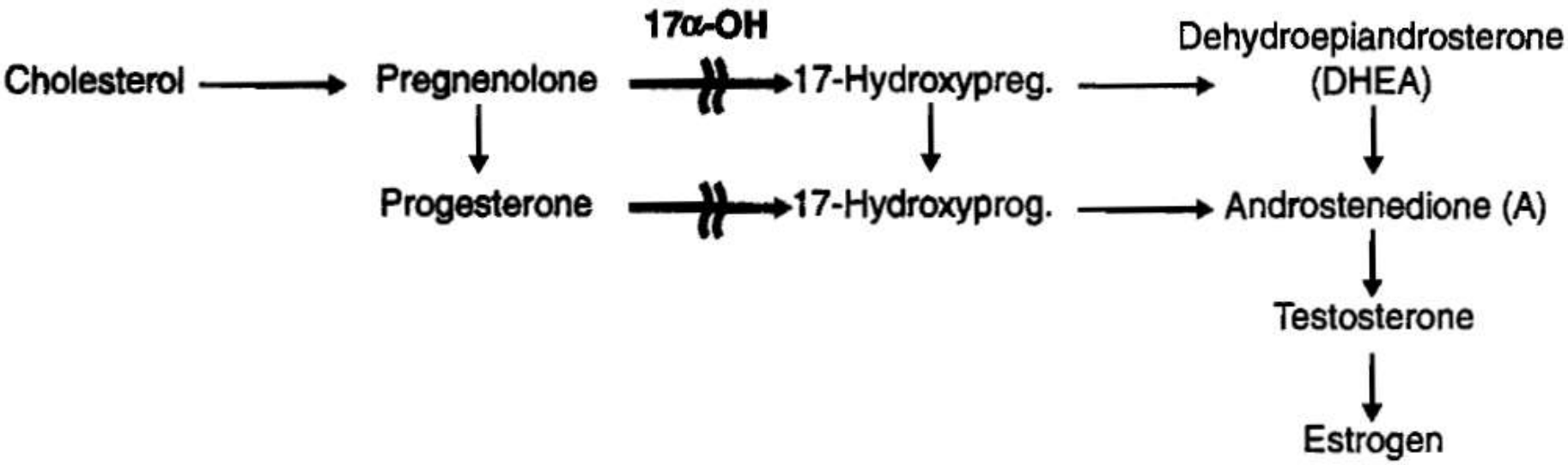


Consequence

Decreased production of testosterone.

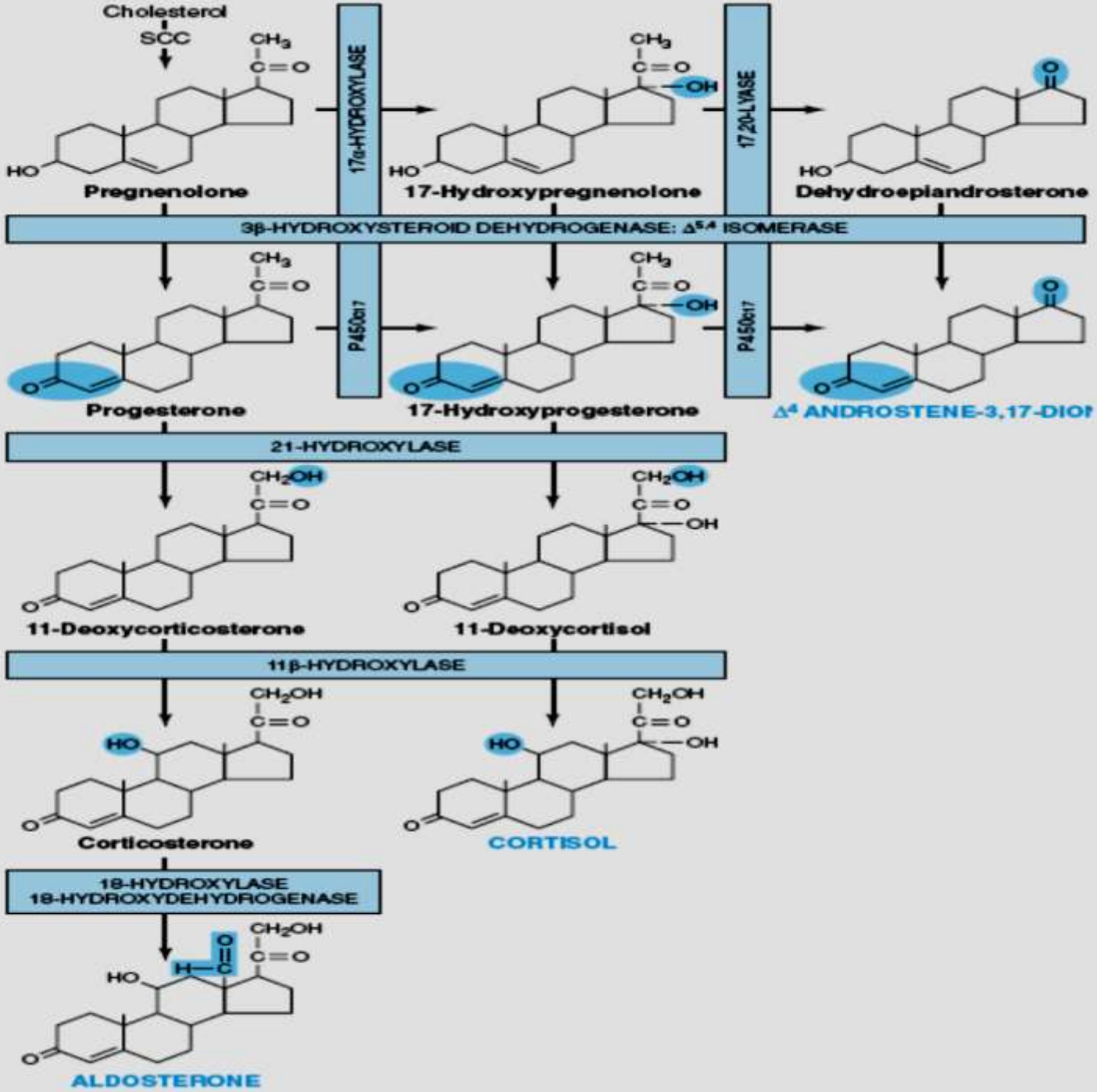
Note: If the loss of androgen is severe, the male fetus will have a problem with the development of male structures.

17α-Hydroxylase Deficiency
Effect in the Ovaries

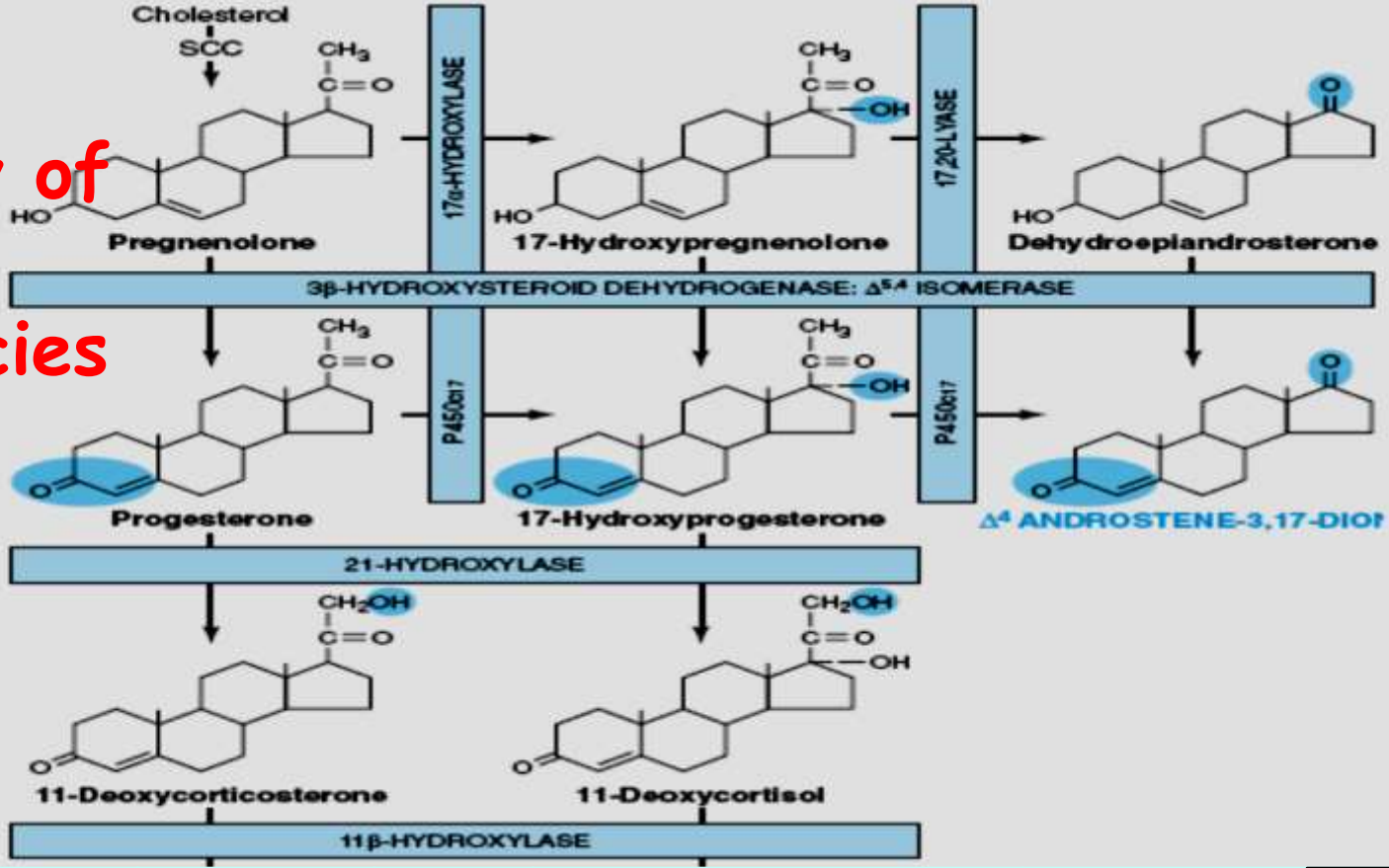


Consequence
Decreased production of estrogens.

- Congenital defects in any of the enzymes leads to deficient cortisol secretion and the syndrome called ***congenital Adrenal hyperplasia,***


Cholesterol
SCC
Pregnenolone
17α-HYDROXYLASE
17-Hydroxypregnenolone
17,20-LYASE
Dehydroepiandrosterone
3β-HYDROXYSTEROID DEHYDROGENASE: Δ5,4 ISOMERASE
Progesterone
P450c17
17-Hydroxyprogesterone
P450c17
Δ4 ANDROSTENE-3,17-DIOI
21-HYDROXYLASE
11-Deoxycorticosterone
11-Deoxycortisol
11β-HYDROXYLASE
Corticosterone
CORTISOL
18-HYDROXYLASE
18-HYDROXYDEHYDROGENASE
ALDOSTERONE

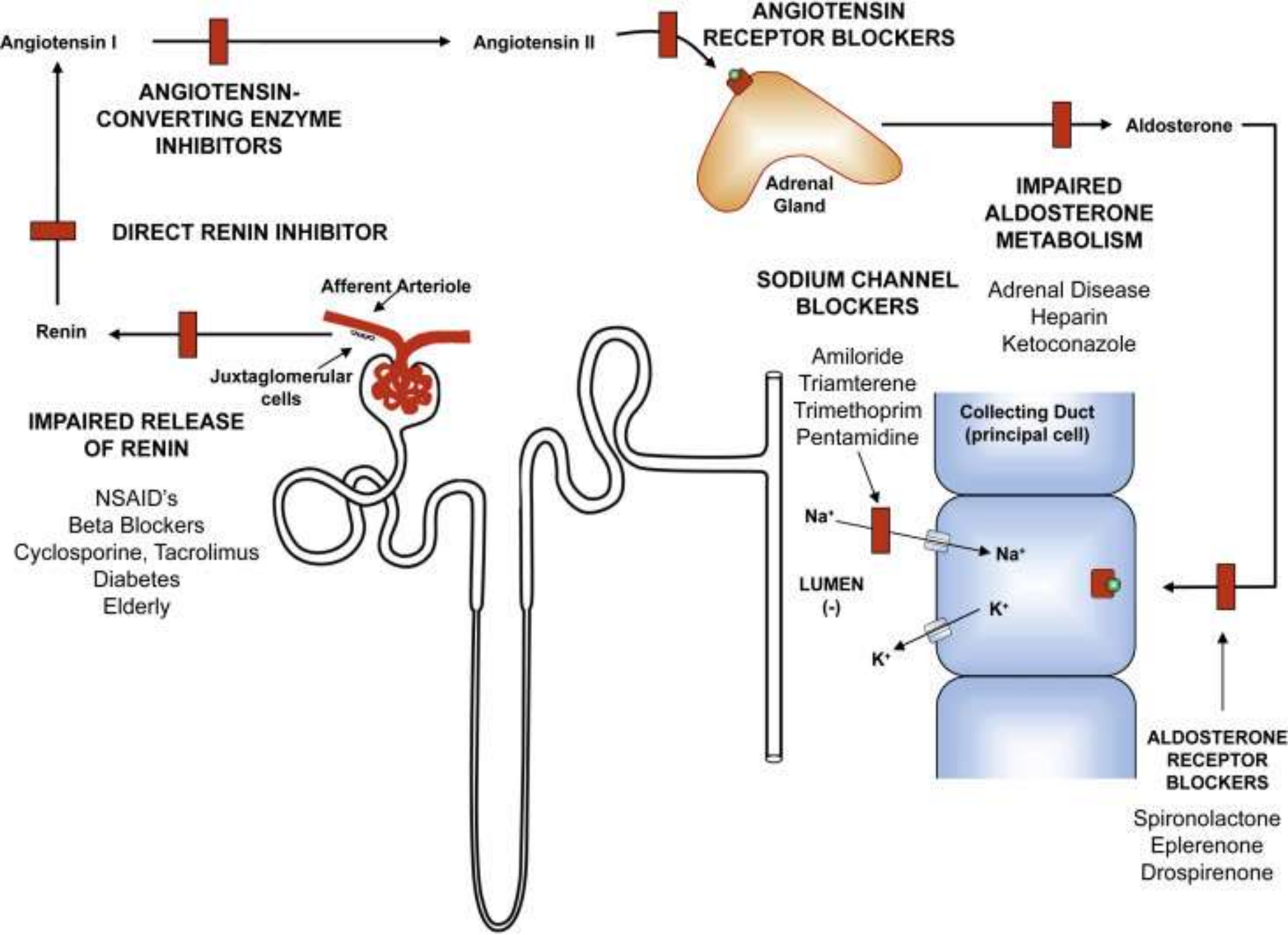
Summary of Enzyme Deficiencies

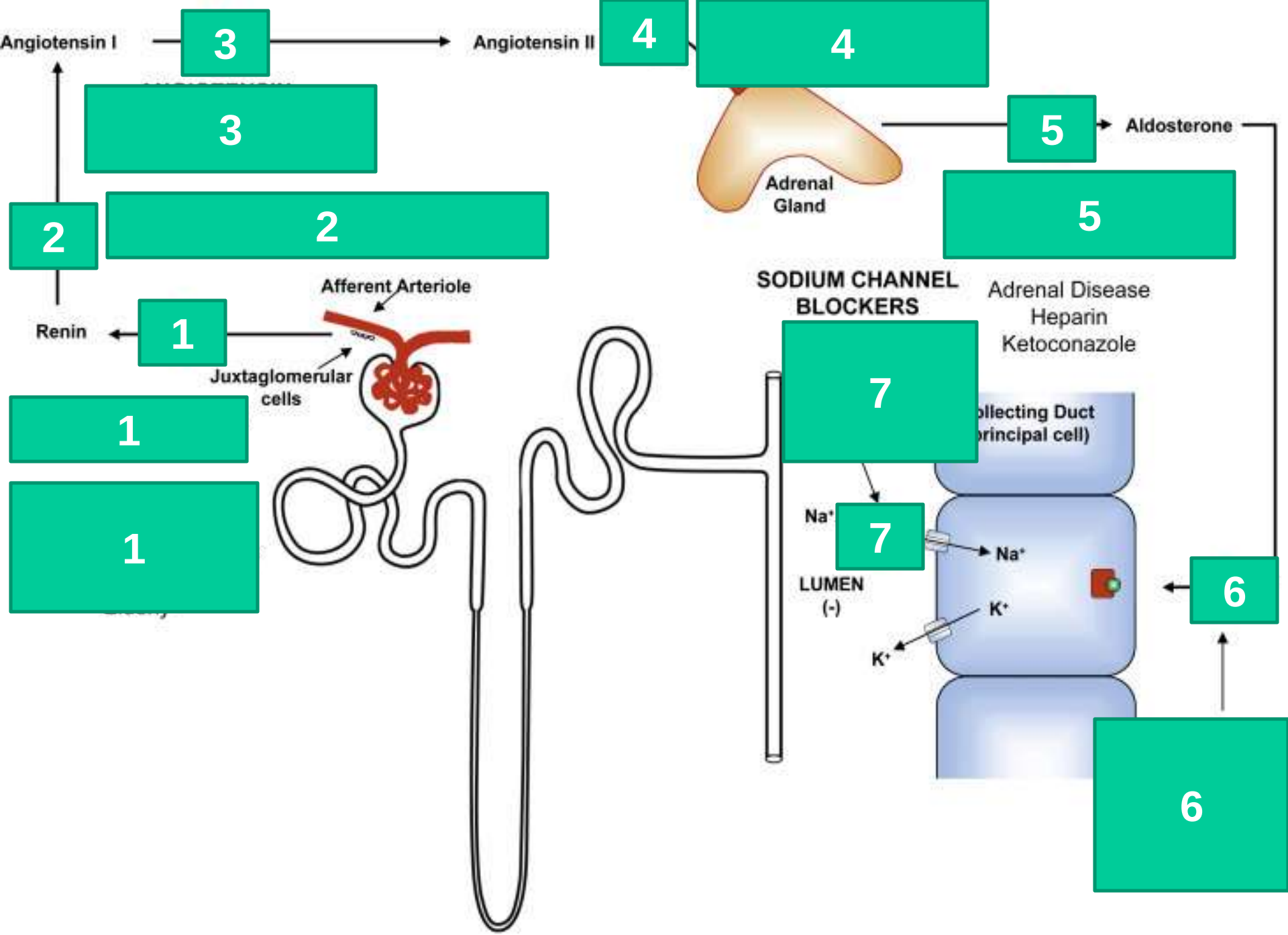


Deficiency	Gluc	ACTH	BP	Mineraloc		Androgen
				Aldo	DOC	

Summary of Enzyme Deficiencies

Deficiency	Gluc	ACTH	BP	Mineraloc		Androgen	
				Aldo	DOC		


Angiotensin I
ANGIOTENSIN-
CONVERTING ENZYME
INHIBITORS
Angiotensin II
ANGIOTENSIN
RECEPTOR BLOCKERS
Adrenal
Gland
Aldosterone
IMPAIRED
ALDOSTERONE
METABOLISM
Adrenal Disease
Heparin
Ketoconazole
DIRECT RENIN INHIBITOR
Renin
Afferent Arteriole
Juxtaglomerular
cells
IMPAIRED RELEASE
OF RENIN
NSAID's
Beta Blockers
Cyclosporine, Tacrolimus
Diabetes
Elderly
SODIUM CHANNEL
BLOCKERS
Amiloride
Triamterene
Trimethoprim
Pentamidine
Collecting Duct
(principal cell)
Na+
Na+
LUMEN
(-)
K+
K+
ALDOSTERONE
RECEPTOR
BLOCKERS
Spironolactone
Eplerenone
Drospirenone


Angiotensin I
3
Angiotensin II
4
4
3
3
5
Aldosterone
Adrenal Gland
5
2
2
Afferent Arteriole
SODIUM CHANNEL BLOCKERS
Adrenal Disease
Heparin
Ketoconazole
Renin
1
Juxtaglomerular cells
7
1
1
Collecting Duct (principal cell)
Na+
7
Na+
LUMEN (-)
K+
K+
6
6

MCQ

- A 63-year-old female presents with muscle weakness, fatigue, and high blood pressure. She is diagnosed as a case of Conn's syndrome by her laboratory investigations. Which one of the following investigations is incompatible with the Conn' syndrome?

a. Decreased levels of DHEA
b. Decreased levels of renin
c. Hypokalemia
d. Increased levels of aldosterone
e. Normal levels of ACTH

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c. Hyperkalemia
d. Increased levels of aldosterone
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MCQ

- A 63-year-old woman was taking anti-hypertensive drugs for the last 10 years. Now for her cholecystitis she was asked for an abdominal u/s that showed bilateral adrenal gland enlargement. From her findings she was diagnosed as case of 17α-Hydroxylase Deficiency. She was given the proper treatment of hydorcortisone. After the appropriate treatment, her blood pressure normalized without anti-hypertensive. Which one of the following has the primary role in bringing her blood pressure to the normal?

a. Decreased aldosterone
b. Decreased ACTH
c. Decreased DOC
d. Decreased corticosterone
e. Decreased renin

MCQ

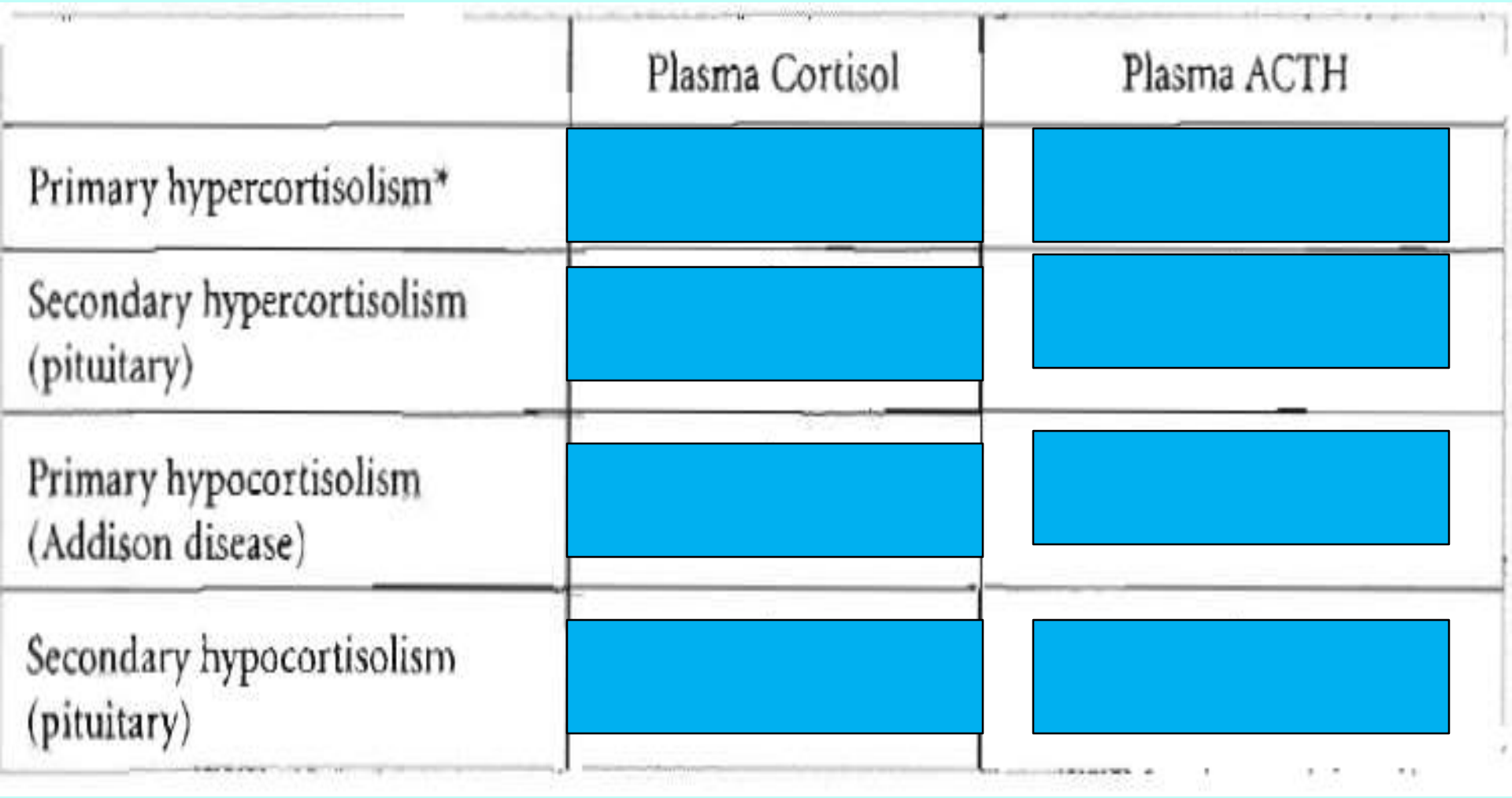
- A 63 years old female has these laboratory investigations; an elevated level of aldosterone, high ACTH, low cortisol, low levels of renin, low dehydroepiandrosterone, and hypokalemia. Which one of the following enzymes is deficient in this patient?

a. 11β-Hydroxysteroid DH
b. 11β-Hydroxylase
c. 17α-Hydroxylase
d. 17,20-lyase
e. 21β-Hydroxylase

MCQ

- Which one of the following findings is Incompatible with all types of congenital adrenal hyperplasia?

a. Enlarged adrenal glands
b. Increased ACTH
c. High androgens
d. Low cortisol
e. Low aldosteron



*Exogenous administration of glucocorticoids produces similar results. There is a suppression of ACTH release, which causes adrenal atrophy.

Which step in steroid hormone biosynthesis, if inhibited, blocks the production of all androgenic compounds but does not block the production of glucocorticoids?

A. Cholestrol ⟶ Pregnenolone
B. Progesterone ⟶ 11 –deoxycorticosterone
C. 17 –Hydroxypregnenolone ⟶ DHEA
D. Testosterone ⟶ estradiol
E. Testosterone ⟶ dihydrotestosterone

A woman has hirsutism, hyperglycemia, obesity, muscle wasting, and increased circulating levels of adrenocorticotropic hormone (ACTH). The most likely cause of her symptoms is:

A. Primary adrenoncortical insufficiency (Addison's disease)
B. Pheochromocytoma
C. Primary overproduction of ACTH (Cushing's disease)
D. Treatement with exogenous glucocorticoids
E. hypophysectomy

Increased adrenocorticotropic hormone (ACTH) secretion would be expected in patients

A. With chronic adrenocortical insufficiency (Addison's disease)
B. With primary adrenocortical hyperplasia
C. Who are receiving glucocorticoid for immunosuppression after a renal transplant
D. With elevated levels of angiotensin II

22. Which step in steroid hormone biosynthesis is stimulated by adrenocorticotropic hormone (ACTH)?

(A) Cholesterol → pregnenolone
(B) Progesterone → 11-deoxycorticosterone
(C) 17-Hydroxypregnenolone → dehydroepiandrosterone
(D) Testosterone → estradiol
(E) Testosterone → dihydrotestosterone

24. Which of the following causes increased aldosterone secretion?

(A) Decreased blood volume

(B) Administration of an inhibitor of angiotensin-converting enzyme (ACE)

(C) Hyperosmolarity

(D) Hypokalemia

26. Propylthiouracil can be used to reduce the synthesis of thyroid hormones in hyperthyroidism because it inhibits oxidation of

(A) Triiodothyronine (T_3)
(B) Thyroxine (T_4)
(C) Diiodotyrosine (DIT)
(D) Thyroid-stimulating hormone (TSH)
(E) Iodide (I^-)

A 35-year-old woman was seen in the emergency room because of recurrent abdominal pain. The history revealed a 2-year pattern of pain in the upper right quadrant, beginning several hours after the ingestion of a meal rich in fried/fatty food. Ultrasonographic examination demonstrated the presence of numerous stones in the gallbladder. The patient initially elected treatment consisting of exogenously supplied chenodeoxycholic acid, but eventually underwent surgery for the removal of the gallbladder, and had a full recovery. The rationale for
the initial treatment of this patient with chenodeoxycholic acid is that this compound:

- interferes with the enterohepatic circulation.
- inhibits cholesterol synthesis.
- increases de novo bile acid production.
- increases cholesterol solubility in bile.